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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,136	Applicant(s) FRASER ET AL.	
	Examin r N. M. Minnifield	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *3-13 and 15-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *3-13 and 15-30* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 3 sheets
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-5 and 14, species SMEZ-2, SEQ ID NO:2, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the Examiner erred in asserting that the amino acid sequence of SPE-J (SEQ ID NO:8) has been disclosed by Goshorn et al. Applicants assert that Goshorn et al only shares 56% identity with SEQ ID NO:8 and refers the Examiner to the IPER (attached Exhibit A). Applicants assert that the Examiner's conclusion that the invention of Group I lacks novelty is erroneous. Applicants assert that the restriction requirement appears to be inconsistent (Group I consist of product and method whereas the other Groups consist of only one invention—a product or a method). Applicants have requested that various groups be combined. Specifically Groups IV and V should be combined with Group I. Group VI should be combined with Group VII. Group VIII should be combined with Group II. Applicants assert that the burden of search is no greater than that is for Group I, VI and Group II respectively. This is not found persuasive because the claims recite "superantigen... or a functionally equivalent variant thereof". It is noted that the IPER states that "The description of the invention in the application does not give an indication of the percentage identity the claimed polypeptide sequences need as a minimum to retain functional equivalence." Therefore bearing this in mind, the documents cited herein are potentially novelty destroying if the above identified identity affords functional equivalence. Applicants are entitled to a first product and a first method using that product, which is set forth in Group I. The remainder of the claimed inventions is restricted as per PCT Rule 13.1 and PCT

Rule 13.2. With regard to burden of search, the restricted Groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. A reference which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other groups. Moreover, as to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Burden in examining materially different groups having materially different issues also exist.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 3-13 and 15-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

3. Claims 1, 2 and 14 will be examined as they are directed to the elected invention and species, Group I and SMEZ-2/SEQ ID NO:2 respectively.

4. The disclosure (see for example pages 7 and 14) is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. drop

Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5. Claims 1 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what are the exact steps of detection, what method is used to detect the absence or presence of the superantigen?

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a superantigen, SMEZ-2, which has an amino acid sequence of SEQ ID NO:2, does not reasonably provide enablement for a superantigen of its amino acid sequence that is a functionally equivalent variant thereof, or a method of subtyping Streptococci using a functionally equivalent variant thereof. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification at page 6 sets forth that functionally equivalent variants, recognizes that it is possible to vary the amino acid sequence of a peptide while retaining substantially equivalent functionality. For example, a peptide can be considered a functional equivalent of another peptide for a specific function if the equivalent peptide is immunologically cross-reactive with and has at least substantially the same function as the original peptide. The specification also sets forth examples of possible amino acid substitutions and that variants can have a greater or lesser degree of homology as between the variant amino acid sequence and the original.

All data on enablement (subtyping) of the superantigen SMEZ-2 is shown with SEQ ID NO:2, not functionally equivalent variants thereof as defined in the specification.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In

view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

It is **not** routine in the art to screen for positions within the protein's sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure (see Bowie et al., Science, Vol 247, pp 1306-1310, especially p. 1306, column 2, paragraph 2 and Kumar et al. PNAS 87: 1337-1341 February 1991. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple deletions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. The specification does not support the broad scope of the claims, which encompass a multitude of polypeptides because the specification does **not** disclose the following :

- the general tolerance to modification and extent of such tolerance;
- specific positions which can be predictably modified;
  -which regions are protective; and
- essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed polypeptides in manner reasonably correlated

with the scope of the claims broadly including any number of deletions, additions, substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The specification does not support the broad scope of the claims which encompass all variants of the polypeptide and possibility of changing one or two amino acids to any one of 23 different amino acids because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity, claimed immunogenicity of the intact polypeptide; and the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Further, Houghten et al teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of

the antibodies..." (p. 24). Houghten et al teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the variants or derivatives that retain immunodominant regions and immunological activity if the regions have been altered. It is known in the art that amino acid changes/variations of a peptide will affect its properties; "... alterations in the chemical nature of an amino acid within a site (e.g., reversal, removal or creation of a charge, elimination of a hydrogen bond, etc.) brought about by chemical modifications or evolutionary replacement in a homologous protein of a different species would reduce or abolish the reactivity of the site." (Bixler et al, p. 56, para. 1). The determination of substitutions, deletions, and other undescribed and/or undefined "modifications" that result in derivatives which retain the immunological activity of the immunodominant region would require undue experimentation for a person of ordinary skill in the art. See M.P.E.P. §§ 706.03(n) and 706.03(z).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamezawa et al (Infection and Immunity, 1997).

The claims are directed to a superantigen, SMEZ-2, which has an amino acid sequence of SEQ ID NO:2 or a functionally equivalent variant thereof.

Kamezawa et al discloses a SMEZ (streptococcal mitogenic exotoxin Z) superantigen from *Streptococcus pyogenes* (abstract). The prior art discloses that these superantigens have a molecular weight range of 25 to 30 kD, a pI of 7 and biological activities include mitogenicity and they act as superantigens to stimulate T cells to produce cytokines (p. 3828, column 1 and materials and methods). Kamezawa et al discloses the amino acid sequence of the superantigen (see figure 5, p. 3832; p. 3831).

The claimed polypeptide appears to be disclosed in the prior art. The prior art polypeptide appears to be the same as claimed. The prior art polypeptide appears to have the same functions (i.e. mitogenic activity, stimulates T cell Receptors) as set forth by Applicants.

Since the Patent Office does not have the facilities for examining and comparing applicants' polypeptide with the polypeptide of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed polypeptide and the polypeptide of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. No claims are allowed.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
March 5, 2003